New protein mutated in neurodegenerative disease

By Robin Arnette

When injury to the mammalian genome occurs, such as when DNA strands break, specialized proteins called poly(ADP-ribose) polymerases, or PARPs, raise an alarm. Upon encountering DNA damage, PARP1 tags a host of DNA damage repair first responder proteins, as a means of controlling their activity. These molecular tags are formed by generating repeating chains of the small molecule ADP-ribose, to create poly(ADP-ribose) or PAR tags.

Proper coordination of responses to DNA damage also requires complete removal and recycling of such tags. For several decades, though, scientists did not know which protein clips the ADP-ribose directly attached to tagged proteins. Now, a team that includes several NIEHS researchers has identified and characterized one such protein, and uncovered another surprising detail — a mutation in its gene leads to a rare form of neurodegenerative disease.

Williams and his collaborators have identified a protein they call TARG1, a new factor in the DNA damage response that's mutated in neurodegenerative disease. (Photo courtesy of Steve McCaw)

Appel helped to determine TARG1's mechanism of action. (Photo courtesy of Steve McCaw)

Working together to find a solution

The research, which appeared online March 12 in The EMBO [European Molecular Biology Organization] Journal, was a multidisciplinary effort from scientists and clinicians from the United Kingdom, United States, Germany, and Iran. Scott Williams, Ph.D., of the NIEHS Laboratory of Structural Biology, led the NIEHS contingent that characterized the activity and structure of the protein, originally known as C6orf130.

Williams said, he and his group were interested in C6orf130, because it is a member of a poorly understood family of proteins that contain ADP-ribose interacting macrodomains. In collaboration with Ivan Ahel, Ph.D., of the Paterson Institute for Cancer Research at the University of Manchester, and Reza Sharifi, M.D., Ph.D., of St. George's University of London, European team members identified a mutation in the *C6orf130* gene.

When the mutated gene was expressed, the resulting C6orf130 protein was chopped in half, rendering it inactive. As a result, people born with two copies of the mutated gene were bound to wheel chairs. They suffered seizures, and displayed a lack of a tendon reflex and a partial absence of a swallowing reflex.

"We renamed C6orf130, terminal ADP-ribose protein glycohydrolase 1, or TARG1, because it cleaves at the stem of where the ADP-ribose modification is made on a protein," Williams said. "The neurodegenerative condition that occurs is a TARG1 deficiency."

So far, the only people who have the unnamed illness come from members of one family in Iran, but Williams said other mutations in TARG1 may produce other infirmities, so more research is needed.

Seeing TARG1 in action

Using X-ray crystallography, as well as a variety of biochemical techniques, Williams' research group, which included Denise Appel, Juno Krahn, Ph.D., and Matthew Schellenberg, Ph.D., generated high-resolution molecular snapshots showing how TARG1 engaged and processed the terminal ADP-ribose. With additional mass spectrometry analysis from Jason Williams, Ph.D., and his group at the NIEHS Protein Microcharacterization Core Facility, the team discovered that TARG1 formed a transient intermediate with its substrate. This transitional molecule was critical in TARG1's removal of ADP-ribose.

Appel is a biologist in the Williams group and shared first authorship on the journal article. She said, defining the molecular mechanism of TARG1 and understanding how one mutation in its gene led to disease was significant, but these studies may also have the potential to help cancer patients.

"Researchers can selectively kill tumor cells by affecting their ability to metabolize poly(ADP-ribose) correctly," Appel said. "Since TARG1 acts to degrade poly(ADP-ribose), it may be an attractive target for drug development in cancer chemotherapy."

Williams was just as excited about the TARG1 research, and said one rarely sees a story laid out in one publication — identification of a critical enzymatic activity and the protein involved, atomic resolution snapshots of its mode of action, and the documentation of the individuals within the human population with defects in that activity.

"It's a fine example of science's move toward powerful multidisciplinary research," Williams said. "It's one of the most

comprehensive projects I've ever been involved in."

Citation: Sharifi R, Morra R, Appel CD, Tallis M, Chioza B, Jankevicius G, Simpson MA, Matic I, Ozkan E, Golia B, Schellenberg MJ, Weston R, Williams JG, Rossi MN, Galehdari H, Krahn J, Wan A, Trembath RC, Crosby AH, Ahel D, Hay R, Ladurner AG, Timinszky G, Williams RS, Ahel I. *(http://www.ncbi.nlm.nih.gov/pubmed/23481255)* 2013. Deficiency of terminal ADP-ribose protein glycohydrolase TARG1/C6orf130 in neurodegenerative disease. EMBO J; doi:10.1038/emboj.2013.51 [Online 12 March 2013].

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